

**A STUDY OF SERUM ZINC LEVELS IN
CHILDREN WITH FEBRILE CONVULSIONS IN
COMPARISON WITH NORMAL AND FEBRILE
CHILDREN**

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CHAPTER - 1

INTRODUCTION

INTRODUCTION

SEIZURES IN CHILDHOOD

A seizure is a paroxysmal time limited change in motor activity and or behaviour that results from abnormal electrical activity in the brain. Seizures are common in pediatric age group and occur in approximately 10% of children ⁽¹⁾. Most seizures in children are provoked by somatic disorders originating outside the brain such as high fever, infection, syncope, head trauma, hypoxia, or toxins. Less than one third of seizures in children are caused by epilepsy, a condition defined as two or more unprovoked seizures occurring at an interval greater than 24hrs apart⁽¹⁾

Infants and children are more prone to have seizures than adults. This reflects the greater neuronal excitability at certain ages as the excitatory glutamate system and inhibitory GABA system do not always balance each other. This results in a tendency to exhibit symptomatic seizures related to high fever, infections, minor asphyxia, medication, bacteria toxins and biochemical disturbances like hyponatremia, hypernatremia, hypocalcemia etc.

TERMINOLOGY⁽²⁾

1. FIT

A fit is the clinical manifestation of cerebral dysrhythmia which may be convulsive as in generalised tonic clonic seizures or non convulsive as in absence seizures.

2. SEIZURE

Seizure is a paroxysmal alteration in behaviour due to any transient brain pathology.

3. CONVULSION

This term is used when a child shows a sudden episode of decerebrate posturing which is followed by clonic jerking.

4. EPILEPSY

Epilepsy is recurrent seizures due to repeated primary cerebral dysrhythmia.

FEBRILE SEIZURES

Febrile seizures are the most common type of seizures observed in the pediatric age group. Although described by ancient Greeks, it was not until this century that febrile seizures was recognized as a distinct

syndrome separate from epilepsy. Almost three decades ago, Livingston⁽³⁾ observed that children with febrile seizures fared better than children with epileptic convulsions not triggered by fever, the prognosis was more favourable and they were more likely to be neurologically normal.

Familiarity with clinical features and long time prognosis of febrile seizures is essential in caring for affected children. Epidemiological studies have been useful in identifying features that carry adverse prognosis and these factors form the basis of proper seizure management and family counseling.

DEFINITION

In 1980, a consensus conference held by “National Institute of Health” described a febrile seizure as “An event in infancy or childhood usually occurring between three months and five years of age associated with fever, but without evidence of intracranial infection or defined cause”.⁽⁴⁾ This definition is useful because it emphasizes age specificity and the absence of underlying brain abnormalities. It does not exclude children with prior neurological impairment and neither provides specific temperature criteria nor defines a seizure. In clinical practice, NIH definition must be interpreted with caution because intracranial infection may not be readily apparent, especially in very young infants.

ILAE DEFINITION

The “International League against Epilepsy” defines febrile seizures as a seizure, occurring in childhood after one month of age associated with febrile illness, not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure and not meeting the criteria for other acute symptomatic seizures.⁽⁵⁾

PATHOPHYSIOLOGY

Febrile seizures occur in young children at a time in their development when seizure threshold is low. They typically occur relatively early in an infectious illness usually during the raise phase of the temperature curve. Rectal temperature may exceed 39.2°C and approximately one fourth of seizure occurs at temperature of greater than 40.2°C. Febrile seizures occur in common childhood infections such as upper respiratory tract infection, lower respiratory tract infection, otitis media, acute gastroenteritis and children respond to these infections with comparably higher temperatures.

Animal studies suggest a possible role of endogenous pyrogens such as interleukin 1 β that by increasing neuronal excitability, may link fever and seizure activity ⁽⁶⁾. Preliminary studies in children support the

hypothesis that the cytokine network is activated and may have a role in pathogenesis of febrile seizures, but the precise clinical and pathological significance of these observations is not yet clear. ^(7,8)

AGE OF ONSET

The onset of febrile seizures generally follows a bell shaped pattern. 94% occur within the first 3 years of age and 6% after 3 years of age. Approximately one half appears during second year of life with peak incidence between 18-24 months. Febrile seizures occurring before 6 months of age should raise the suspicion of serious infections like bacterial meningitis. Febrile seizures after 5 years of age should be managed cautiously because benign causes are less common in older children.

GENETICS

Genetic influences play a major role in febrile seizures. In a child with febrile seizures risk is 10% for the sibling and risk increases to 50% for the sibling if a parent has febrile seizures as well ⁽¹⁰⁾. Tsuboi et al in 1987 reported a concordance rate of 56% in monozygotic twins and 14% in dizygotic twins. Although clear evidence exists for a genetic basis of febrile seizures, exact mode of inheritance is unclear ⁽⁹⁾. While polygenic inheritance is likely, a small fraction of families are identified with an

autosomal dominant pattern of inheritance leading to the description of ‘febrile seizure susceptibility trait’ with autosomal pattern of inheritance with reduced penetrance. Candidate genes in these families include both sodium and GABA channel mutations. Linkage studies in several families have mapped the febrile seizure gene to chromosome 19p and 8q 13-21. Febrile seizures represent a good example of interplay between genetic susceptibility and environmental factors. Most likely, all children have some increased susceptibility to seizures from fever at the specific age window, this being increased markedly by an underlying genetic influence.

GEOGRAPHIC DISTRIBUTION

In the United States 2-5% of children have febrile seizures by their fifth birthday. Similar rate of febrile seizure is found in Western Europe. The incidence elsewhere in the world varies between

5-10% in India

8% in Japan

14% in Guam

0.5-1.5% in China ⁽¹¹⁾

SEX DISTRIBUTION

Some studies demonstrate a slight male preponderance⁽⁹⁾.

TYPES OF FEBRILE SEIZURE

A simple febrile seizure is generalised, tonic clonic in nature, lasts for a few seconds and rarely upto 15 min, is followed by a brief period of postictal drowsiness and occurs only once in 24 hrs ⁽¹⁾.

A febrile seizure is described a complex or complicated when the duration is >15 min, when repeated convulsions occur within 24 hrs, or when focal seizure activity or focal findings are present during the postictal period ⁽¹⁾.

ILLNESS ASSOCIATED WITH FEBRILE SEIZURES

Viral illness is the predominant cause of febrile seizures. Rantala et al in 1995 has reported upper respiratory infection as the triggering cause of febrile seizures in 67% of children. Other common illness associated with febrile seizures include gastroenteritis, middle ear infections and lower respiratory infections. Febrile seizures in conjunction with shigellosis constitute the most frequent extra intestinal manifestation of this infection. A direct neurotoxic effect of the shigella bacterium on seizure threshold had been proposed. Immunization related seizures also manifest with fever usually within 48hrs of inoculation. Data from “National Collaborative Perinatal Project” indicated that age of onset,

personal and family histories and clinical presentations resemble those of febrile seizures from infectious causes.

RISK FACTORS FOR RECURRENCE

About one third of children with a first febrile seizure experience recurrent seizures ⁽¹²⁾.

The risk factors are as follows: ^(13, 14)

- Younger age at time of first febrile seizure.
- Relatively low fever at time of first seizure.
- Family history of febrile seizure in a first degree relative.
- Brief duration between fever onset and initial seizure.
- Multiple initial febrile seizures during the same episode.

Age of onset is the most important predictor of febrile seizure recurrence. One half of infants younger than one year of age at the time of their first febrile seizure will have a recurrence compared with 20% of children older than 3 years.

Shorter duration of fever before the initial febrile seizure and lower temperature at onset are associated with increased risk of recurrence ⁽¹⁴⁾.

Fever	Recurrence Risk
< 1 hr.	44%
1-24 hrs.	24%
>24 hrs.	13%

With each 1°C rise of temperature from 101°F to 105°F, recurrence risk decreases from 35% to 13% respectively ⁽¹⁴⁾.

RISK FACTORS FOR EPILEPSY

Data from five large cohorts of children with febrile seizures indicate that epilepsy subsequently develops in 2%-10% of children who experience febrile seizures ⁽¹⁵⁾. In most studies, the risk of developing epilepsy after a single simple febrile seizure is not different from the risk of this disorder in the general population. The factors that are associated with greater risk of epilepsy include: ⁽¹⁶⁾

- The presence of complex features during the seizure or postictal period
- Positive family history of epilepsy
- An initial febrile seizure before 12 months of age
- Delayed developmental milestones or a preexisting neurological disorder.

The incidence of epilepsy is >9% when several risk factors are present compared with an incidence of 1% in children who have febrile convulsions and no risk factors ⁽¹⁷⁾.

FEBRILE SEIZURES-MORBIDITY AND MORTALITY

The mortality associated with febrile seizure is extremely low. No deaths were reported from the National Collaborative Perinatal Project⁽¹⁸⁾ or the British Cohort Study ⁽¹⁹⁾. These projects could not find any evidence of permanent motor deficits after febrile seizures. The cognitive abilities of children with febrile seizures have been extensively studied; The Collaborative Perinatal Project found no difference in IQ scores at the age of 7 years between children with febrile seizures and their siblings ⁽¹⁸⁾. A recent study from Taiwan ⁽²⁰⁾ in addition to comparing intelligence and behaviour, also found no difference in memory between children with febrile seizures including complex ones. This finding is significant because febrile seizures appear to be of limbic origin and memory is subserved by the hippocampus.

INVESTIGATIONS

To make a diagnosis of febrile seizure, one must exclude meningitis, encephalitis and other neurological illness.

The most common issue in the emergency department is whether lumbar puncture is needed. The incidence of meningitis in children with febrile seizure is between 2%-5% ⁽²¹⁾. In one series, Joffe and associates reported that children with meningitis were found to have risk factors viz a visit for medical care within the previous 48 hrs, focal seizures or suspicious findings on physical or neurological examination.

The American Academy of Pediatrics issued guidelines for the neurodiagnostic evaluation of the child with simple febrile seizure between the ages of 6 months and 5 years. It recommended a lumbar puncture in the infant younger than 12 months of age. The child between 12 and 18 months of age, in the absence of suspicious history or findings on examination, does not require a lumbar puncture. However some studies suggest that lumbar puncture is not needed for children with first episode of simple febrile seizure ⁽²²⁾.

CT brain should be considered in patients with complex febrile seizures. A study by Teng et al showed presence of intracranial pathology in 4% of patients with complex febrile seizures ⁽²³⁾.

Electro encephalograms are of limited value in the evaluation of the child with febrile seizures. There is no evidence that they help predict either

recurrence of febrile seizures or the development of subsequent epilepsy
(24).

TREATMENT

TERMINATING A FEBRILE SEIZURE

Intravenous diazepam or lorazepam is effective in most cases. Rectal diazepam or diazepam gel is also appropriate for use in a prehospital setting and in cases in which intravenous access is difficult. If the seizure activity continues after an adequate dose of benzodiazepine, then a full status epilepticus protocol should be used⁽²⁵⁾.

PREVENTING A FEBRILE SEIZURE

ANTIPYRETICS

Aggressive treatments with antipyretic medications are indicated to reduce the risk of having a febrile seizure. Little evidence is however available to suggest that antipyretic agents reduce the risk of recurrent febrile seizure⁽²⁶⁾.

BENZODIAZEPINES

Diazepam given orally at 1 mg/kg/day at the onset of febrile illness for 2-3 days will reduce the probability of a febrile seizure⁽²⁶⁾.

BARBITURATES

Intermittent therapy with phenobarbitone at the onset of fever is ineffective in reducing the risk of recurrent febrile seizures.

CONTINUOUS PROPHYLAXIS

Phenobarbital, given daily at dose of 3-5 mg/kg/day to achieve a blood level of 15mcg/ml was effective in reducing the risk of recurrent febrile seizures in several well-controlled trials. However these studies also demonstrated adverse effects, primarily hyperactivity that required discontinuation of therapy ⁽²⁷⁾.

Daily treatment with valproate also has been found to be effective in reducing the risk of recurrent febrile seizures. However the potential risks of fatal hepatotoxicity especially in children less than 2 years of age do not justify its use in a disorder with excellent prognosis regardless of treatment ⁽²⁷⁾.

Phenytoin and carbamazepine are ineffective in preventing recurrent febrile seizures in humans and in animal models of hyperthermia induced seizures.

TRACE ELEMENTS IN FEBRILE CONVULSIONS

A number of trace elements are said to play a role in febrile convulsions by their co-enzyme activity or ability to influence ion channels and receptors. Studies have shown that iron, zinc, selenium, copper and magnesium play a significant role in febrile convulsions.

Zinc (Zn) acts as a co-factor of glutamic acid decarboxylase, an enzyme which maintains the production of GABA in central nervous system and decreased level of Zn in CSF has also been observed in febrile seizure ^{(28), (29)}.

Magnesium (Mg) is also involved in neuronal function and inhibits the facilitatory effects of calcium on synaptic transmission and exerts a voltage dependent blockage of N-methyl-D-aspartate (NMDA) receptor channel.

Copper (Cu) inhibits Mg^{++} -adenosine triphosphatase(ATPase) and Na^{+} - K^{+} -ATPase enzymes and disturbs the sodium and potassium homeostasis, which results in genesis of epileptiform discharges ⁽³⁰⁾.

Iron insufficiency may play a role in the development of first febrile seizures in children. Researchers found that plasma ferritin levels were lower in children with a first febrile seizure than in children who had febrile illnesses without convulsions ⁽³¹⁾.

ZINC

FUNDAMENTAL FACTS

Atomic Weight	65
Total body zinc	35.4 μ mol/L
Zinc in fat free tissues	30 μ g/g
Zinc in bones	200 μ g/g
Zinc in hair	125 to 250 μ g/g
Plasma zinc	80 to 110 μ g/dl

Total body zinc is primarily intracellular thus proportional to lean body mass. The largest body stores of zinc of about 200 μ g/g are present in the bones. This is sequestered and does not form a part of metabolic pool.

SOURCES OF ZINC ⁽³²⁾

Zinc content of food varies widely. Very good sources of zinc are red meat and sea foods. Other good animal sources are poultry, pork and dairy products. Whole grains and vegetables represent good plant sources of zinc. Poor zinc sources are fruits and refined cereals.

Traditional staple foods like cereals legumes and tubers contain zinc but the presence of phytate, fiber and lignin reduces its bioavailability. In addition to dietary food sources, endogenous sources for zinc are pancreatic and biliary secretions released into gastro intestinal tract.

Food	Zinc Level in mg/100g
Sea Food	
Oysters	17-19
Crab meat	3.8-4.3
Poultry & Meat	
Liver	3.1 – 3.9
Beef	3.9 – 4.1
Pork	1.6 – 2.1
Egg & Dairy Products	
Egg	1.1 – 1.3
Milk	0.4 – 0.6
Cheese	2.8 – 3.2
Legumes	0.6 – 1.0
Grams & Cereals	
Rice & Pasta	0.3 – 0.6
Bread	0.6 – 0.8
Vegetables	0.1 – 0.7
Fruits	<0.1

ABSORPTION

Zinc balance is maintained by rate of absorption from the intestines and rate of excretion into intestines. Mechanism of absorption is not well understood. Zinc absorption is enhanced by glucose, lactose and soya protein. Zinc is better absorbed from human milk than cow's milk. Fiber and phytates decrease zinc absorption. Copper and cadmium compete with zinc for carrier protein. Folic acid may reduce zinc absorption when zinc intake is low. Vegetables and fruits contribute very little dietary intake.

REQUIREMENTS ⁽³³⁾

The age wise zinc requirements as suggested by the “Sub committee on the 1989, 10th edition of the RDA” are as follows:

Infants	5mgs
Children	10 mgs
Women	12 mgs
Pregnant women	15 mgs
Lactating women	16 mgs
Men	15 mgs

METABOLIC ROLE OF ZINC

Zinc is an essential trace element for plants animals and micro organism. In human beings, zinc plays ubiquitous biological roles ⁽³⁴⁾. Zinc plays a crucial role in the functioning of about 300 enzymes. A few of zinc dependent enzymes include carbonic anhydrase, alkaline phosphatase, carboxy peptidase, superoxide dismutase, phospholipase C etc.

Zinc plays an important role in tissue or cell growth. This is related primarily to its function in the regulation of protein synthesis as well as synthesis and catabolism of nucleic acids. With respect to transcription, zinc appears to interact with nuclear proteins that bind to promoter sequences of specific genes. Zinc forms a structural component of zinc fingers which recognize DNA base sequences during replication and transcription of DNA.

Zinc also regulates expression of the metallothionein gene, apoptosis and synaptic signaling.

Zinc is essential for normal function of neutrophils, natural killer cells, monocytes and macrophages.

Zinc plays an important role in regeneration of intestinal mucosa, wound healing and epithelial cell turnover. These functions explain why zinc plays such an important part in the protection against infections.

ZINC AND CENTRAL NERVOUS SYSTEM

Zinc containing presynaptic vesicles was first discovered by Finn-Mogens Haug in 1967. The hippocampus was found to have the highest concentration of zinc, in the brain, approximately 30 μ /g dry weight.

In the CNS, zinc acts as a neurosecretory product or cofactor ⁽³⁵⁾. Zinc is highly concentrated in the synaptic vesicles of a specific contingent of neurones called “Zinc containing” neurons. Zinc containing neurons are a subset of glutamatergic neurons. The colocalisation of zinc and glutamate implies that zinc is involved in the function of the glutamatergic synapses. Zinc increases the storage capacity of glutamate or slows the release rate of glutamate.

Apart from this, zinc also stimulates the activity of pyridoxal kinase, which is involved in the synthesis of pyridoxal phosphate from pyridoxal ⁽³⁶⁾. Pyridoxal phosphate in turn stimulates the activity of glutamic acid decarboxylase which catalyses GABA synthesis from glutamate. Zinc may also interact with postsynaptic receptors to facilitate GABA action.

Hence, a decrease in zinc concentration results in lowering of GABA level which can precipitate seizures.

Zinc also modulates the activity of glutamate on its receptors and facilitates the inhibitory effect of calcium on N-Methyl-D – aspartate receptors, thus preventing the excitatory neuronal discharge ⁽³⁷⁾. Thus in hypozincemia, NMDA receptors are activated inducing an epileptic discharge in febrile children.

LABORATORY ASSESSMENT OF ZINC

The determination of plasma or serum zinc concentration by atomic absorption spectrophotometry is the most reliable test for routine assessment of zinc levels. Zinc level is estimated by the method of Fernandes et al (1971). This method describes the determination of zinc in serum. Samples are diluted with deionised water. The analysis is performed against standards prepared with glycerol to approximate the viscosity characteristics of the diluted samples.

REAGENTS

1. **Glycerol Diluent:** 50ml of reagent grade glycerol was diluted to 1000 ml with deionised water.
2. **Standard Solution of Zinc:** Zinc metal 0.5g exactly was dissolved in minimal volume of (1+1) Hcl. Then the solution was diluted to 1 litre with 1% Hcl with concentration of 500µg/ml.
3. **Working standard of zinc:** 80µl of stock solution was diluted to 100 ml of de-ionised water.
4. **Sample preparation:** Serum sample was diluted 10 times with de-ionised water and analysed.

ANALYSIS

1. Serum samples were brought to room temperature and then gently mixed by inverting the tubes.
2. Deliver 0.5 ml of specimen or control into a 16mm plastic test tube, 2.0 ml of de-ionised water was added and mixed immediately.

3. The instrumental and gas flow setting and aspiration rate are established to optimise signal and the background noise was minimised.
4. The glycerol diluent was aspirated into the flame of the instrument and the baseline was read to zero absorbance. The baseline drift was corrected by aspirating the glycerol diluent before and after each aspiration of standard and specimen.
5. The zinc's working standards were sequentially aspirated from most dilute, to most concentrated till the reading is stable. The resulting values are used to establish the working curve.
6. Then the serum sample and control are aspirated into the Atomic absorption spectrometer.
7. The serum zinc concentration is calculated by using the absorbance reading by interpolation from the working curve.

SUITABLE INSTRUMENT CONDITIONS

Mineral	Zinc
Hallow Cathode Lamp	Zn
Wavelength	213.9
Flame Type	Air Acetylene
Slit Setting	0.2 nm
Linear Working Range	0.5 µg/ml
Relative Noise	1.0

The values are expressed as µg/dl

The accepted reference interval for plasma zinc is 70 to 110 µg/dl.

CHAPTER 2

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Mahyar et al did a case control study at Qazvin University at Iran comparing 52 children between 9 months and 5 years with first episode of febrile convulsions with 52 healthy children in the same age group. The mean age of onset of febrile convulsions in this study was 27 months. The mean serum zinc level in the patient group was 62.8mcg/dl and in the control group was 85.7mcg/dl. The difference was statistically significant indicating that hypozincemia predisposes to febrile convulsions.⁽³⁸⁾

Gunduz et al studied the serum and CSF zinc levels in 20 children with febrile convulsions between 9 months and 5 years and 20 children between 6 months and 14 years with fever without convulsions. The mean age of onset of convulsions in this study was 25 months. In the patient group the mean serum and CSF zinc levels were 69.8mcg/dl and 68mcg/dl respectively. In the control group the serum and CSF zinc levels were 105.4mcg/dl and 116mcg/dl respectively. The difference was statistically significant implying that zinc levels in the serum as well as CSF are decreased in children with febrile convulsions.⁽³⁹⁾

F.Ehsani pour et al studied the serum zinc level in three groups of children between 6 months and 5 yrs. Group A consisted of 34 children with febrile convulsions, Group B consisted of 40 children with fever alone and Group C consisted of 18 children with non-Febrile convulsions.

The mean serum zinc levels of Group A, Group B, and Group C were 76.8mcg/dl, 90.1mcg/dl and 94.5mcg/dl respectively. The serum zinc level of the febrile convulsions group was significantly lower than the other two groups. Another significant finding in this study was that children with fever had significant lower zinc levels than the children with Non-Febrile convulsions. This study concluded that serum zinc level decreases during infection and this decrease was more significant in patients with febrile convulsions. ⁽⁴⁰⁾

Heydarian farhad et al did a case control study on 60 patients aged between 6 months and 6 years in iran.30 patients had simple febrile convulsions and 30 patients had fever without convulsions.The mean serum zinc level was 66.3 mcg/dl and 75.8 mcg/dl in the case group and control group respectively which was statistically significant⁽⁴¹⁾

Ganesh et al conducted a case control study at a tertiary care private hospital in Chennai comparing 38 cases of simple febrile convulsions and 38 age matched controls (fever alone) .The mean serum zinc levels in cases and controls were 32.17 mcg/dl and 87.6mcg/dl respectively. This study concluded that Indian children with febrile convulsions had low serum zinc levels. The mean age of onset of convulsions in this study was 23.8 months and no significant difference in serum zinc levels was found with relation to age, sex and degree of fever ⁽⁴²⁾

Palliana et al conducted a similar study at tertiary hospital in Mumbai comparing serum zinc levels of 75 children aged 6 months to 5 years admitted with first episode of febrile convulsions with that of children admitted with fever alone. The mean serum zinc level in cases and controls were 81.84mcg/dl and 90.38mcg/dl respectively which was statistically significant.⁽⁴³⁾

Mojtaba amiri et al studied serum selenium, zinc and copper levels in children with febrile convulsion and healthy children. The mean serum zinc levels were 66.9mcg/dl and 107.8mcg/dl among cases and controls respectively. The serum selenium levels were 44.9mcg/l and 62.8mcg/l among cases and controls respectively. There was no difference in the copper levels of the two groups. This study showed that both decreased serum zinc and selenium levels play a role in febrile convulsions⁽⁴⁴⁾

Mollah et al studied zinc in the CSF of patients with febrile convulsions and compared it with that of children with fever without convulsions. The mean CSF zinc levels in cases and controls were 40.19mcg/dl and 74.98mcg/dl respectively.

He concluded that significantly lower zinc levels exist in CSF in children with febrile convulsions. However no relationship was found between CSF zinc status and age, sex, duration of fever and time of lumbar puncture after convulsions⁽²⁸⁾

CSF concentration of zinc, magnesium, copper and gamma amino butyric acid in febrile convulsions were studied by **OP Mishra et al** at Banaras Hindu University at Varanasi India. The study used two controls namely patients with encephalitis and patients with fever with meningismus. The mean CSF and serum zinc, magnesium, copper values were significantly decreased in febrile convulsions in comparison to encephalitis and fever with meningismus. No significant changes were observed in serum and CSF copper levels among the three groups⁽²⁹⁾.

CHAPTER 3

AIMS & OBJECTIVES

AIMS AND OBJECTIVES

AIM OF THE STUDY

To determine whether children with febrile convulsion have decreased serum zinc level when compared to normal children and children with fever without convulsions.

STUDY JUSTIFICATION

Numerous studies have been done to analyse the role of trace elements in febrile convulsions. Studies have shown that hypozincemia predisposes to febrile convulsions and many such studies have been done in Iran, Turkey and Bangladesh. Two studies done in India one at Chennai and one at Mumbai have shown similar results. However both the studies have been done in large Metropolitan cities where the study population may not be representative of the Indian population which is predominantly rural. This study has been done Chengalpattu medical college which is the main health care institution to more than hundred villages in and around Chengalpattu. Due to the paucity of the Indian studies especially in the rural population we undertook this study at our hospital.

PLACE OF STUDY

Chengalpattu Medical College – Paediatric Department

DESIGN OF STUDY

Descriptive Study.

PERIOD OF STUDY

October 2009 to October 2010.

SAMPLE SIZE

Sample size of 50 was selected for each group viz,

Children with febrile convulsions,

Children with fever without convulsions,

Normal Children.

INCLUSION CRITERIA

- Children aged six months to five years with first episode of simple febrile convulsions.
- Children aged six months to five years with fever without convulsions.
- Normal healthy children between six months to five years.

EXCLUSION CRITERIA

The following children were excluded from the study.

- Cerebral palsy
- Seizure disorder
- Chronic diseases
- Weight <70% of expected
- Complex febrile seizure
- Children on zinc preparations
- Recurrent febrile seizure
- Children on anti convulsants

CHAPTER 4

MATERIALS AND METHODS

MATERIALS AND METHODS

This descriptive study was conducted during October 2009 to October 2010 at Chengalpattu Medical College, a tertiary care teaching hospital in Chengalpattu.

The materials used in this study were acid propylene washed test tubes, IV cannula, scalp vein set, Test tube stand, centrifuge, serum collection test tubes, and refrigerator.

This study included 150 children aged between 6 months and 5 years among which 50 had presented with first episode of simple febrile seizures, 50 had fever without seizures and 50 were healthy.

Informed consent of the parents of the three groups of children was obtained in a printed consent form in tamil as the predominant population was illiterate. Any questions or doubts were cleared by the examining physician in Tamil and the signature of the parent or left hand thumb impression was obtained.

The study protocol was approved by the ethics committee of our hospital.

Prior to inclusion of the children in the study, a detailed history of the presenting complaints were recorded which included duration of fever,

time of onset of seizures, type of seizures, duration of seizures, past history of seizures and family history of seizures. In addition, history suggestive of any triggering factors for the febrile episode like cough and cold, nasal discharge, ear discharge, burning micturition or crying during micturition were also recorded.

Vital signs namely heart rate; respiratory rate and blood pressure were measured and recorded. The axillary temperature was recorded in all children with the mercury thermometer placed in the axilla for three minutes.

Anthropometric measurements namely weight, height, mid-arm circumference and head circumference were recorded. Those children whose weight less than 70% of expected, Height less than 12.5 cm, mid arm circumference less than 12.5 cm (Applicable for children 1-4 years of age) and head circumference less than the third centile were excluded.

This was followed by general examination and systemic examination in detail. Those children who showed features of any chronic congenital or acquired illnesses were excluded. Those who showed features suggestive of intracranial infection like altered sensorium, meningeal signs, bulging anterior fontanel etc were also excluded.

Three milliliters of whole blood was collected by venipuncture under strict aseptic precautions in sterile metal free acid propylene washed plastic test tube. The sample was allowed to stand without any disturbance for five hours to enable settling down of erythrocytes. Then the serum was separated by centrifuging at 2500 revolutions per minute under aseptic conditions. The serum alone was removed and transferred to acid washed plastic collection tube which was properly labeled. The tube was sealed tightly and stored in the freezer compartment of the refrigerator till transfer to Madras Veterinary College at Vepery where the zinc levels were measured. The serum zinc levels were measured by atomic absorption spectrometry –Perkin Elmer Model 2380 as per the procedure already described. The analyzing personnel were blinded with regard to the clinical details of the samples in order to prevent investigator bias.

Though earlier studies have established a linear relationship between serum zinc and CSF zinc levels in children with febrile seizures, CSF zinc analysis was not done in our study. The cases in our study had only simple febrile seizures and on ethical grounds CSF analysis was not done in the children with fever alone and normal healthy children.

CHAPTER 5

ANALYSIS & RESULTS

STATISTICAL ANALYSIS AND RESULTS

This study was conducted at chengalpattu medical college to compare the serum zinc levels in three groups of children namely children with febrile convulsions ,children with fever alone and normal children.The data collected was entered by a data entry operator and analysed by a statistician using SPSS software. The following test statistics were used in the analysis.

1. Chi Square test.
2. Two sample T test.
3. Bivariate Correlations.
4. One way analysis of Variance.

The baseline characteristics of the three groups of children were compared as follows

DEMOGRAPHIC DATA

AGE DISTRIBUTION

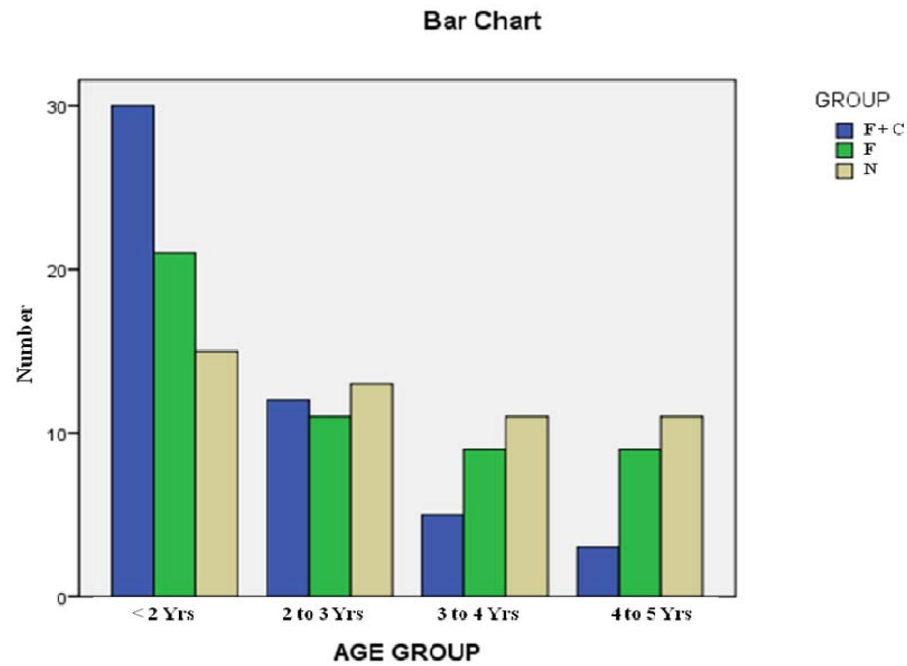
AGE GROUP		GROUP			
		F+C	F	N	Total
< 2 yrs	Number	30	21	15	66
	% within GROUP	60.0%	42.0%	30.0%	44.0%
2 to < 3 yrs	Number	12	11	13	36
	% within GROUP	24.0%	22.0%	26.0%	24.0%
3 to < 4 yrs	Number	5	9	11	25
	% within GROUP	10.0%	18.0%	22.0%	16.7%
4 to <= 5 yrs	Number	3	9	11	23
	% within GROUP	6.0%	18.0%	22.0%	15.3%
Total	Number	50	50	50	150
	% within GROUP	100.0%	100.0%	100.0%	100.0%

P=0.060 not significant

In the febrile convulsions group 60% of children were below 2 years of age, 24% between 2 to 3 yrs, 10% between 3 to 4 yrs and 6% were between 4 to 5 yrs of age.

In the fever group 42% were below 2 yrs of age, 22% between 2 to 3 yrs, 18% between 3 to 4 yrs and 18% were between 4 to 5 yrs of age.

In the normal group 30% were below 2 yrs of age, 26% between 2 to 3 yrs of age, 22% between 3 to 4 yrs of age and 22% were between 4 to 5 yrs of age.



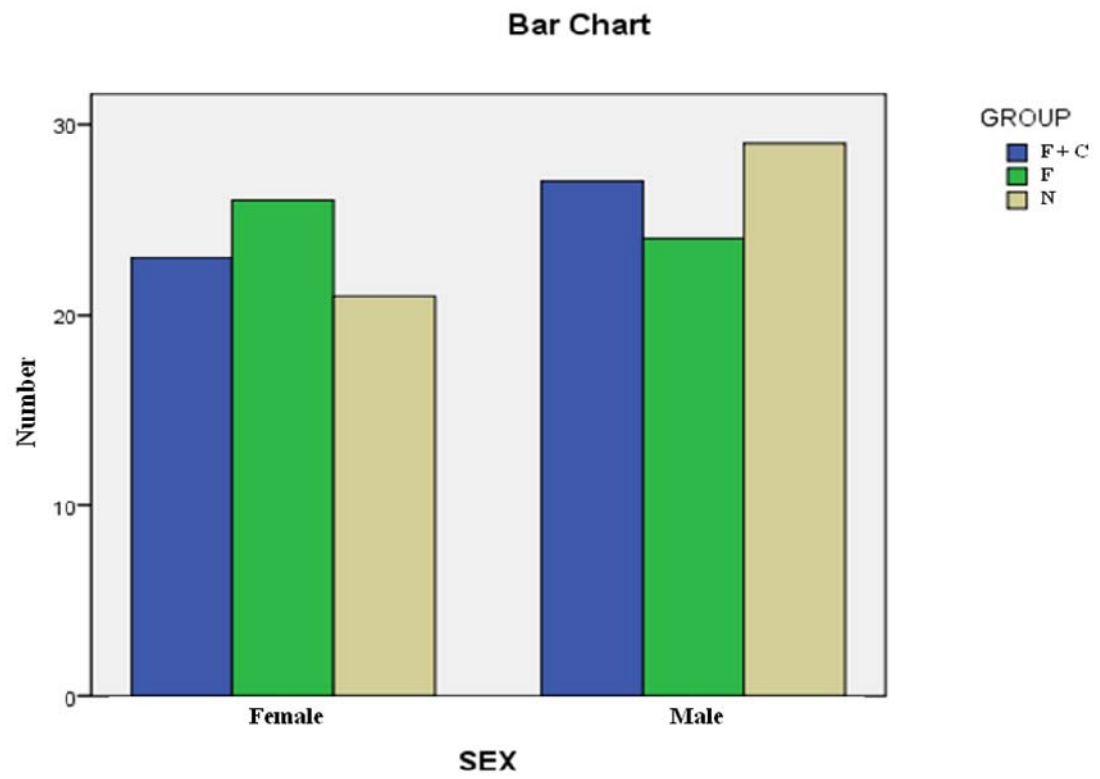
The three groups were comparable with respect to age distribution.

SEX DISTRIBUTION

SEX		GROUP			Total
		F+C	F	N	
F	Number	23	26	21	70
	% within GROUP	46.0%	52.0%	42.0%	46.7%
M	Number	27	24	29	80
	% within GROUP	54.0%	48.0%	58.0%	53.3%
Total	Number	50	50	50	150
	% within GROUP	100.0%	100.0%	100.0%	100.0%

P=0.601 not significant.

- Among children with febrile convulsions 46% were females 54% were males.
- Among children with fever 52% were females 48% were males.
- In the 3rd group of normal children 42% were females 58% were males.



The three groups were comparable with respect to sex distribution.

SOCIOECONOMIC STATUS (SES)

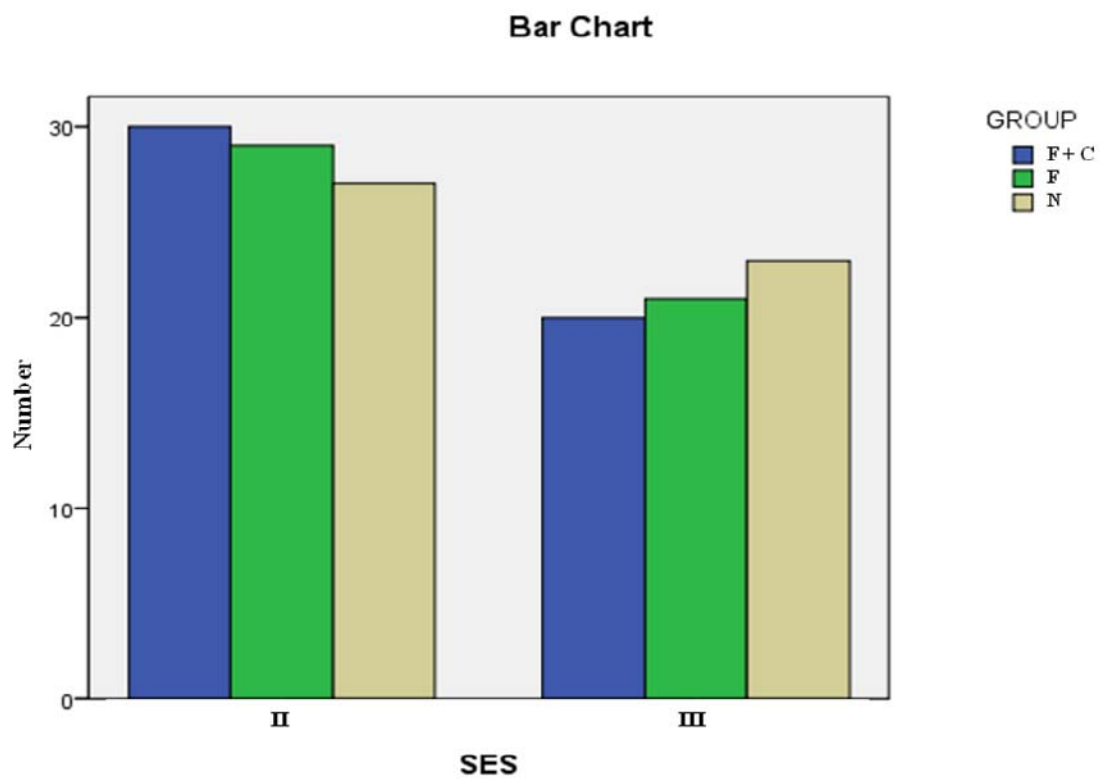
SOCIOECONOMIC STATUS		GROUP			Total
		F+C	F	N	
II	Number	30	29	27	86
	% within GROUP	60.0%	58.0%	54.0%	57.3%
III	Number	20	21	23	64
	% within GROUP	40.0%	42.0%	46.0%	42.7%
Total	Number	50	50	50	150
	% within GROUP	100.0%	100.0%	100.0%	100.0%

P=0.826 not significant.

In the febrile convulsions group 60% belong to kuppusamy class II, 40% belong to kuppusamy class III.

In the fever group 58% belong to class II & 42% belong to class III.

In the normal children group 54% belongs to class II & 46% belong to class III.



The three groups were comparable with respect to distribution of children among class II & class III Socioeconomic status.

FAMILY HISTORY

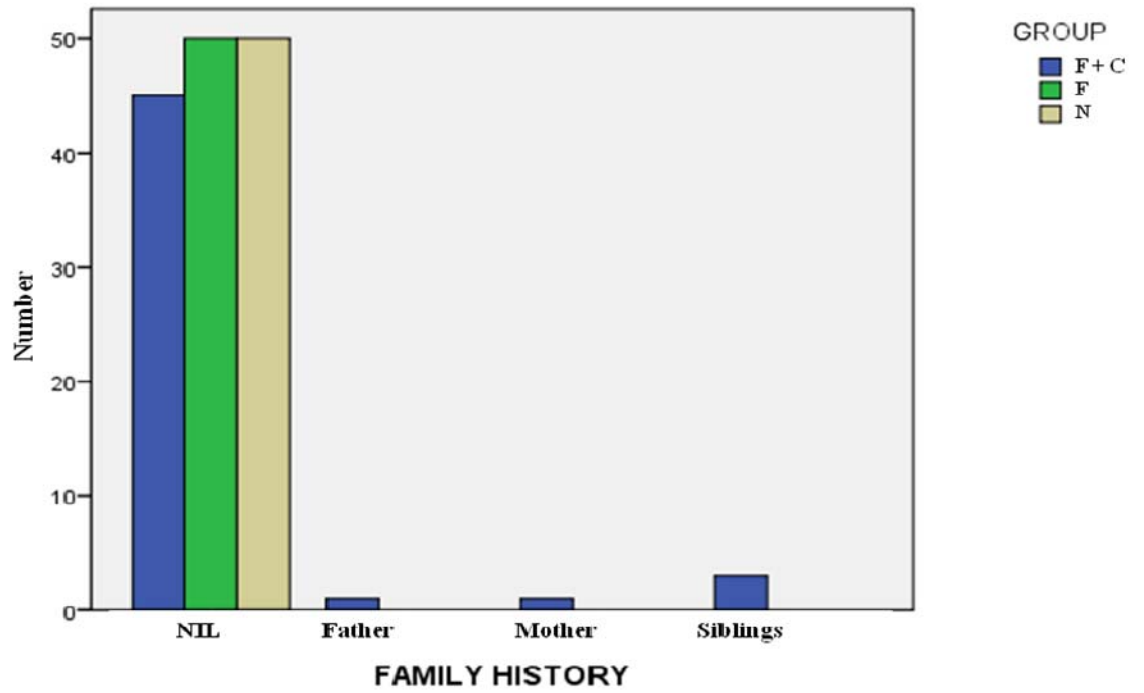
FAMILY HISTORY		GROUP			Total
		F+C	F	N	
NIL	Number	45	50	50	145
	% within GROUP	90.0%	100.0%	100.0%	96.7%
Father	Number	1	0	0	1
	% within GROUP	2.0%	.0%	.0%	.7%
Mother	Number	1	0	0	1
	% within GROUP	2.0%	.0%	.0%	.7%
Siblings	Number	3	0	0	3
	% within GROUP	6.0%	.0%	.0%	2.0%
Total	Number	50	50	50	150
	% within GROUP	100.0%	100.0%	100.0%	100.0%

P=0.111(not significant)

In the febrile convulsions group 90% of the children did not have positive family history of febrile convulsions.

One child had positive family history of febrile convulsions in the father one had similar history in the mother & three children gave positive family history in the siblings. In the other two groups none of them had positive family history of febrile convulsions.

Bar Chart



NUTRITIONAL STATUS

NUTRITIONAL STATUS		GROUP			
		F+C	F	N	Total
GRADE 1 PEM	Number	26	25	28	79
	% within GROUP	52.0%	50.0%	56.0%	52.7%
NORMAL	Number	24	25	22	71
	% within GROUP	48.0%	50.0%	44.0%	47.3%
Total	Number	50	50	50	150
	% within GROUP	100.0%	100.0%	100.0%	100.0%

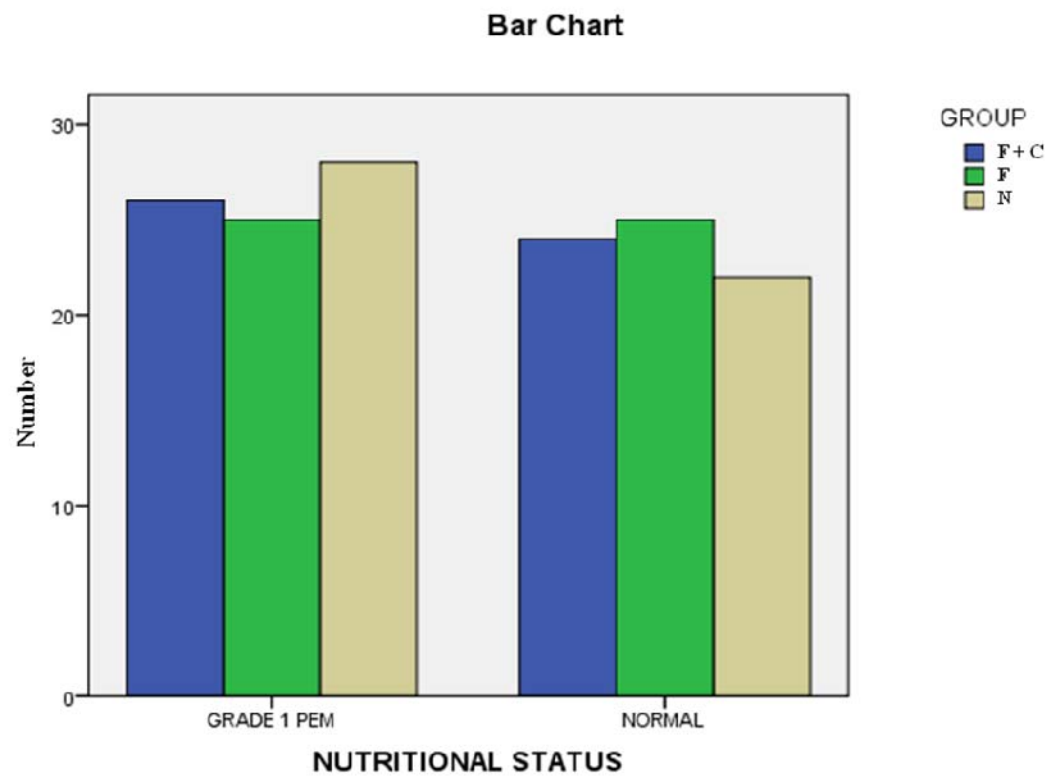
P=0.829 not significant.

Only children with weight for expected more than 70% were included in our study as children with severe malnutrition may have coexistent micronutrient deficiencies.

In the febrile convulsions group 48% had normal nutritional status, 52% had grade I PEM.

In the fever group 50% had normal nutritional status and 50% had grade I PEM.

In the normal group 44% had normal nutritional status and 56% had grade I PEM.



The children in the three groups were comparable with respect to their nutritional status.

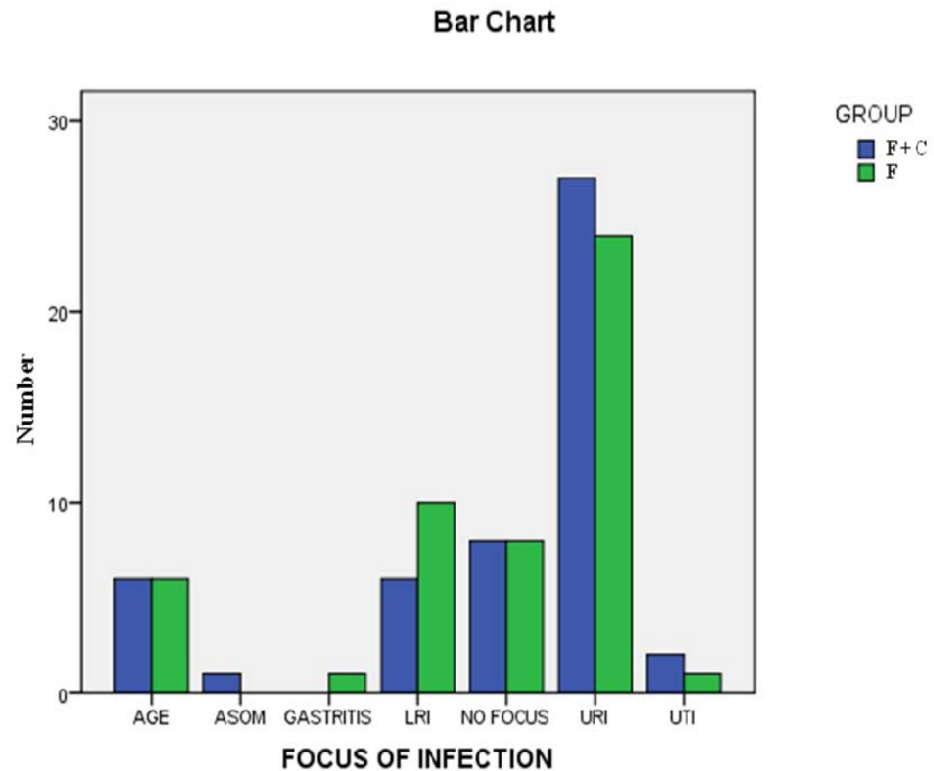
FOCUS OF INFECTION

FOCUS OF INFECTION			GROUP		Total
			F+C	F	
	AGE	Number	6	6	12
		% within GROUP	12.0%	12.0%	12.0%
	ASOM	Number	1	0	1
		% within GROUP	2.0%	.0%	1.0%
	GASTRITIS	Number	0	1	1
		% within GROUP	.0%	2.0%	1.0%
	LRI	Number	6	10	16
		% within GROUP	12.0%	20.0%	16.0%
	NO FOCUS	Number	8	8	16
		% within GROUP	16.0%	16.0%	16.0%
	URI	Number	27	24	51
		% within GROUP	54.0%	48.0%	51.0%
	UTI	Number	2	1	3
		% within GROUP	4.0%	2.0%	3.0%
	Total	Number	50	50	100
		% within GROUP	100.0%	100.0%	100.0%

P=0.743 not significant.

Upper respiratory tract infection was found to be the triggering illness for febrile convulsion in 27 children out of 50 constituting 54%. Incidence of acute gastroenteritis, acute suppurative otitis media, lower

respiratory tract infection, urinary tract infection was found to be 12%, 2%, 12%, & 4% respectively. No localising signs were found in 16% of the children.



ANALYSIS OF FEBRILE CONVULSIONS GROUP

	MEAN	STD. DEVIATION
AGE	1.89	.937
AXILLARY TEMPERATURE	102.5760	.71530
SERUM ZINC LEVEL microgram/dl	42.9380	6.85110
FEVER SEIZURE INTERVAL	7.5900	5.36303

Mean age of onset of febrile convulsions was found to be 1.8 years i.e 20 months.

Mean axillary temperature at the time of convulsion was 102.5 degree F.

The mean fever seizure interval was found to be 7.5 hrs.

The mean serum zinc level in this group was found to be 42.9 mcg/dl

CORRELATION		SERUM ZINC LEVEL microgram/dl
AGE	Pearson Correlation	.195
	Sig. (2-tailed)	.174
	N	50
AXILLARY TEMPERATURE	Pearson Correlation	.167
	Sig. (2-tailed)	.245
	N	50
FEVER SEIZURE INTERVAL	Pearson Correlation	.223
	Sig. (2-tailed)	.119
	N	50

Bivariate correlation test were used for the variables age, axillary temperature, fever seizure interval with respect to serum zinc level. From

above table, there is no correlation between the above said parameters and serum zinc level.

SERUM ZINC LEVEL & NUTRITIONAL STATUS

NUTRITIONAL STATUS		N	MEAN	STD. DEVIATION	STD. ERROR MEAN
SERUM ZINC LEVEL (microgram/dl)	Grade 1 PEM	26	43.5577	6.11883	1.20000
	Normal	24	42.2667	7.64180	1.55988

P=0.511 not significant.

Mean serum zinc level was 43.5mcg/dl among normal children & 42.2mcg/dl among children with grade I PEM. There is no significant variation with nutritional status of the children.

SERUM ZINC LEVEL AND FAMILY HISTORY

FAMILY HISTORY		N	MEAN	STD. DEVIATION	STD. ERROR MEAN
SERUM ZINC LEVEL (microgram/dl)	Present	5	43.6600	3.49042	1.56096
	Absent	45	42.8578	7.14828	1.06560

P=0.807 not significant.

The mean serum zinc level in children with positive family history was 43.6mcg/dl where as in children with no family history in the mean value was 42.8 mcg/ dl. Thus there is no statistically significant difference with reference to family history.

SERUM ZINC LEVEL AND SEX OF THE CHILD

SEX		N	MEAN	STD. DEVIATION	STD. ERROR MEAN
SERUM ZINC LEVEL (microgram/dl)	M	27	43.6704	7.48665	1.44081
	F	23	42.0783	6.07214	1.26613

P=0.418 not significant.

The mean serum zinc level among male & female children with febrile convulsions was 43.6mcg/dl & 42mcg/dl respectively. This difference is not statistically significant.

ANALYSIS OF FEVER GROUP

DESCRIPTIVE STATISTICS

	MEAN	STD. DEVIATION	N
AGE	2.42	1.197	50
AXILLARY TEMPERATURE	102.2700	.86902	50
SERUM ZINC LEVEL (microgram/dl)	70.0380	5.07334	50

CORRELATION		SERUM ZINC LEVEL (microgram/dl)
AGE	Pearson Correlation	-.096
	Sig. (2-tailed)	.507
	N	50
AXILLARY TEMPERATURE	Pearson Correlation	-.055
	Sig. (2-tailed)	.703
	N	50

GROUP STATISTICS

NUTRITIONAL STATUS		N	MEAN	STD. DEVIATION	STD. ERROR MEAN
SERUM ZINC LEVEL (microgram/dl)	Grade 1 PEM	25	67.2000	4.19682	.83936
	Normal	25	72.8760	4.26109	.85222

P=.324 (not significant)

Similarly serum zinc level was not found to vary significantly with age axillary temperature nutritional status or sex of the child in children who presented with fever alone.

SERUM ZINC LEVEL IN THE THREE GROUPS

SERUM ZINC LEVEL (microgram/dl)

					95% CONFIDENCE INTERVAL FOR MEAN	
	N	MEAN	STD. DEVIATION	STD. ERROR	LOWER BOUND	UPPER BOUND
F+C	50	42.9380	6.85110	.96889	40.9909	44.8851
F	50	70.0380	5.07334	.71748	68.5962	71.4798
N	50	71.3640	5.62185	.79505	69.7663	72.9617
Total	150	61.4467	14.38832	1.17480	59.1252	63.7681

P=0.0000< 0.0001 significant.

The mean serum zinc level in children with febrile convulsions was 42.9mcg/dl. The serum zinc level in children with fever and normal children was 70mcg/dl & 71mcg/dl respectively.

On comparing the serum zinc level among the three groups statistical significance was obtained between children with febrile convulsions & the other two groups namely normal children and children with fever alone. Thus decreased serum zinc level is a significant predisposing factor for febrile convulsions. By using Posthoc Multiple comparisons test we came to know that the Fever convulsion group is significantly different from fever and normal group. There is no significant difference between fever and normal group.

CORRELATIONS

		SERUM ZINC LEVEL (microgram/dl)
AGE	Pearson Correlation	.195
	Sig. (2-tailed)	.174
	N	50
AXILLARY TEMPERATURE	Pearson Correlation	.167
	Sig. (2-tailed)	.245
	N	50
SERUM ZINC LEVEL microgram/dl	Pearson Correlation	1
	Sig. (2-tailed)	
	N	50
FEVER SEIZURE INTERVAL	Pearson Correlation	.223
	Sig. (2-tailed)	.119
	N	50

Bivariate correlation test were used for the variables age, axillary temperature, fever seizure interval with respect to serum zinc level. From above table, there is no correlation between the above said parameters and serum zinc level.

CHAPTER 6

DISCUSSION

DISCUSSION

This study was conducted to determine whether children with febrile convulsion had low serum zinc levels compared to children with fever alone and normal children. The three groups of children were comparable with respect to age, sex, nutritional status and socioeconomic status.

The mean age of febrile convulsions was 20 months in this study. Lynette et al reported a mean age of 18 months and all other studies reported mean age of onset between 20 and 25 months ⁽⁴⁵⁾.

Positive family history was present in 10% of children with febrile convulsion in this study. This is significantly less when compared to other studies. Siddique et al reported an incidence of 30% in his study ⁽⁴⁶⁾. Saidul haque in 1981 reported 20% of children with positive family history in his study ⁽⁴⁷⁾. Farwell in 1994 reported positive family history in 29% of cases ⁽⁴⁸⁾. However the finding that children with positive family history had earlier age of onset of febrile convulsions shown in these studies was present in our study also. The mean age of onset was 17.8 months in children with positive family history which is less compared to 20 months as a whole. Similar findings were reported by Plochl et al in 1992 ⁽⁴⁹⁾

Viral illnesses are the predominant cause of febrile convulsions. In this study upper respiratory tract infection was found to be the triggering illness in 54% of children. Acute gastroenteritis and lower respiratory tract

infection contributed 12% each and urinary tract infection contributed 4%. In 16% of children there were no localizing signs associated with fever. Upper respiratory tract infection as the most common trigger was also reported in studies done by Rantala et al in 1995 and Mahyar et al in 2010.

(50)

The mean serum zinc levels were 42.9mcg/dl, 70mcg/dl and 71.3mcg/dl in children with febrile convulsions, children with fever alone and normal healthy children. Children with febrile convulsions have statistically significant low serum zinc levels when compared to children with fever and normal children. Children with fever did not show a significant decrease in serum zinc level compared to normal children which is similar to the findings of Ganesh et al⁽⁴²⁾. However Ehsanipour et al has shown that serum zinc levels are decreased in children with fever though the magnitude of decrease was not as much as in febrile convulsions.

The serum zinc levels did not show any significant correlation with age of onset sex, axillary temperature or the fever – seizure interval in our study. All the previous studies have shown similar findings in this aspect.

In our study the mean serum zinc level in normal children was found to be 71.3mcg/dl which is the lower limit of the normal reference level of 70 to 110mcg/dl. The mean serum zinc level in the Mahyar study⁽³⁸⁾ and

Mojtaba study ⁽⁴⁴⁾ were 85.7mcg/dl and 107.8mcg/dl respectively. The mean serum zinc level in children with fever in our study is 70mcg/dl which is again less than the corresponding values reported by Ganesh et al ⁽⁴²⁾ and Palliana et al ⁽⁴³⁾. As the serum zinc level in any population is influenced by factors such as dietary pattern, vitamin A and Vitamin D deficiency, zinc levels in the soil and water, further studies are need in this aspect to identify the probable cause for this finding. ^(51,52)

CHAPTER 7

CONCLUSION

CONCLUSION AND RECOMMENDATION

This study shows that serum zinc levels are decreased in children with febrile convulsions, thus indicating that zinc deprivation plays a significant role in the pathogenesis of febrile convulsions.

Zinc has already been recommended by the WHO as a part of management of acute watery diarrhoea. The role of zinc in febrile convulsions should be investigated by further studies and if the results are reproducible zinc supplementation should be extended to other common paediatric conditions like febrile convulsions, pneumonia etc.

However considering the fact that zinc has multiple beneficial roles in the body system, zinc supplementation may still serve as a cost effective measure for prevention of febrile convulsions in the susceptible age group especially in the presence of positive family history.

CHAPTER 8

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BIBLIOGRAPHY

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PROFORMA

NAME:

AGE:

S.NO:

SEX:

ADDRESS:

SOCIO ECONOMIC STATUS:

DIET:

HISTORY:

DATE / TIME OF ONSET OF FEVER:

TIME OF ONSET OF SEIZURES:

TYPE OF SEIZURES:

DURATION OF SEIZURES:

NO OF EPISODES:

ANY POSTICTAL DEFICIT:

DEVELOPMENTAL HISTORY:

FAMILY HISTORY:

PAST HISTORY:

GENERAL EXAMINATION

VITAL SIGNS

HR:

RR:

BP :

TEMP:

ANTHROPOMETRY:

HT:

WT:

HC:

CC:

MAC:

COMMENT:

SYSTEM'S:

CNS:

CVS:

RS:

P/A:

INVESTIGATION:

SERUM ZINC:

OTHERS: